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Lactate and D-Dimer levels in acute pulmonary embolism and COVID-19

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Abstract

Aim: This study aimed to compare clinical data and laboratory results in patients examined for suspected pulmonary embolism (PE) in the emergency department based on three groups: patients with coronavirus disease-2019 (COVID-19), patients with PE and patients with both COVID-19 and PE.

Material and Methods: This retrospective study was approved by the local ethics committee of the university. Patients included in the study were divided into three groups: Group 1, consisting of COVID-19-polymerase chain reaction (PCR) (negative) and PE (positive) patients; Group 2, consisting of COVID-19-PCR (positive) and PE (negative) patients, and Group 3, consisting of COVID-19-PCR (positive) and PE (positive) patients.

Results: The three patient groups included in the study had no difference in terms of age ($p = 0.916$) or sex. The laboratory results of the groups were compared using the Kruskal–Wallis test, which showed significant differences in the levels of white blood cells ($p = 0.005$), lymphocytes ($p < 0.001$), neutrophils ($p = 0.016$), D-Dimer ($p < 0.001$) and lactate ($p = 0.001$). Receiver operating characteristic curve analysis with a cut-off value of >2590 for D-Dimer showed 71.43% specificity and 78% sensitivity in differentiating Group 1 from Group 2, and with a cut-off value of >3640, it had 80% specificity and 81.82% sensitivity in differentiating Group 3 from Group 2.

Discussion: COVID-19 leads to increased incidence of PE. In addition to clinical data, D-Dimer and lactate levels can be used in the differentiation of these patients.

Keywords
COVID-19, D-Dimer, Lactate, Pulmonary Embolism

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Introduction

Coronavirus disease-2019 (COVID-19) has a clinical picture ranging from a completely asymptomatic form of the disease to acute respiratory distress syndrome with rapidly progressive clinical deterioration associated with high mortality rates [1]. In patients diagnosed with COVID-19, thrombotic complications, such as pulmonary embolism (PE), deep vein thrombosis, ischaemic stroke and myocardial infarction cause significant morbidity and mortality [2]. Studies have reported PE to be a common complication in patients with COVID-19, with an incidence rate as high as 5%–19% [3].

Since the beginning of the COVID-19 pandemic, studies have reported high levels of D-Dimer and high rates of pulmonary thromboembolism in patients with COVID-19 [4]. Abnormal coagulation parameters, including high levels of D-Dimer and fibrin degradation products, have been found to be strongly correlated with in-hospital mortality in patients hospitalized with severe COVID-19 [5].

PE may present with classical manifestations, such as sudden-onset shortness of breath and pleuritic chest pain in the emergency room, as well as with insidious-onset shortness of breath developing over days to weeks or with other symptoms less related to respiration, such as syncope. Clinicians need to have a high degree of suspicion for PE in patients presenting with potential cardiopulmonary symptoms because the consequences of missed or delayed diagnosis of PE can be serious [6]. PE is suspected based on clinical symptoms, risk factors and D-Dimer in the emergency department. Computed tomography pulmonary angiography (CTPA) is the preferred method of imaging in the diagnosis of PE [7]. However, clinical pre-test probability scores, such as the Wells' criteria [8], have been reported to be unreliable in predicting PE in patients with COVID-19 [9]. Assessment of D-Dimer levels has been reported to be potentially helpful in improving risk stratification for PE, but its exact value is yet to be clarified [10].

Risk factors associated with severe COVID-19 are also risk factors for PE. D-Dimer levels increase in both PE and COVID-19, and PE and COVID-19 frequently occur concomitantly. All these factors pose a challenge for emergency physicians.

This study sought to compare the initial clinical data and laboratory results for patients admitted to the emergency department with respiratory symptoms based on three groups: patients who had only COVID-19, patients who had only PE and those who had both COVID-19 and PE.

Material and Methods

This retrospective study was approved by the local ethics committee of the university. The study included patients who presented to the emergency department of a university hospital with respiratory complaints between January 01, 2020 and December 31, 2021 and who underwent CTPA imaging with suspicion of PE. Patient characteristics were recorded on detailed data forms prepared for this purpose. The data were extracted from the hospital's electronic record system. The CTPA protocol was performed after intravenous injection of 50–75 mL of high-concentration iodinated contrast medium at a flow rate of 3–4 mL/s using a multi-detector scanner [11]. Patients' electronic medical records were used to identify those who had COVID-19 confirmed via coronavirus polymerase chain reaction (PCR) of nasopharyngeal or oropharyngeal swab samples. The patients were divided into three groups: Group 1, consisting of COVID-19-PCR (negative) and PE (positive) patients; Group 2, consisting of COVID-19-PCR (positive) and PE (negative) patients; and Group 3, consisting of COVID-19-PCR (positive) PE (positive) patients.

Creatinine (Crea, 0.6–1.2 mg/dL), C-reactive protein (CRP, 0–0.5 mg/dL), urea (10–50 mg/dL) and procalcitonin (0–0.05 ng/mL) levels were measured at the Biochemistry Laboratory of the University Hospital and run on the Advia 2400 Chemistry system (Siemens Diagnostics, Tarrytown, NY, USA). Hematological parameters, including white blood cell count (WBC, 3.8–8.6 103/mm3), hemoglobin (11.1–17.1 mg/dL), hematocrit (HCT, 33%–57%), platelets (140–360 103/mm3), lymphocytes (1.3–3.5 10e3/μL) and neutrophils (2.1–6.1 10e3/μL), were measured using the Advia 2120i (Siemens, Germany) automated analyzer. Plasma D-Dimer (0–0.55 mg/L), prothrombin time (PTT, 10.5–15.5 s.), activated partial thromboplastin time (aPTT, 22–36 s.) and the international normalized ratio (INR, 0.8–1.2) were measured using the Sysmex CS5100 device (Sysmex, Japan). Lactate analysis was performed using a standard point-of-care full blood gas analysis assay (ABL 800 FLEX analyzer; Radiometer Medical ApS, Copenhagen, Denmark). All the tests assigned by the autoanalyzer were performed immediately on the collected serum samples. Informed consent was obtained from all individuals included in this study.

Statistical Analysis

Statistical analysis of the data was performed using SPSS 21.0 (IBM Corporation, Armonk, NY, USA) and MedCalc (Version 10.1.6.0, Ostend, Belgium) software suite. In the data analysis, the Shapiro–Wilk normality test was used to check the distribution of continuous variables. Numerical data were expressed as median (IQR) and qualitative data as a percentage. The Kruskal–Wallis test was used to compare the three groups. The Kruskal–Wallis test was followed by post-hoc Dunn's test for pairwise comparisons. In the comparison of categorical data, the Pearson chi-square test was used if <20% of the cells had theoretical frequency of <5 and the exact test was used if >20% of the cells had theoretical frequency of <5. Receiver operating characteristic (ROC) curve analysis was performed to check the usefulness of D-Dimer and lactate levels in differentiating among the groups. ROC curve analysis results were expressed as % specificity and % sensitivity [area under the ROC curve (AUC), p, 95% confidence interval (CI)]. The significance level was set at $p < 0.05$ in all analysis results.

Results

There was no difference in age ($p = 0.916$) and sex distribution among the three patient groups included in the study. Comparison of laboratory results among the groups using the Kruskal–Wallis test found significant differences in the levels of WBC ($p = 0.005$), lymphocyte ($p < 0.001$), neutrophils ($p = 0.016$), D-Dimer ($p < 0.001$) and lactate ($p = 0.001$) (Table 1).

Levels of WBC, lymphocyte, neutrophil, D-Dimer and lactate, which were found to be significantly different among the groups according to the Kruskal–Wallis test, were analyzed with pairwise comparisons using the post-hoc Dunn's test. The

results showed significant differences between Group 1 and Group 2 in terms of WBC (p = 0.006), lymphocyte (p < 0.001), neutrophils (p = 0.009), D-Dimer (p < 0.001) and lactate (p = 0.002) levels, significant differences between Group 1 and Group 3 in terms of lymphocyte (p = 0.019), neutrophil (p = 0.028) and lactate (p = 0.029), but no significant differences in WBC and D-Dimer levels. Comparison of Group 3 with Group 2 patients found a significant difference in only D-Dimer (p ≤ 0.001) levels, but no significant difference in WBC, lymphocyte, neutrophils or lactate levels (Table 2).

ROC analysis with a cut-off value of >2590 for D-Dimer showed 71.43% specificity and 78% sensitivity in differentiating Group 1 from Group 2. With a cut-off value of >3640, it had 80% specificity and 81.82% sensitivity in differentiating Group 3 from Group 2, and with a cut-off value of >9670, it had 96% specificity and 39.39% sensitivity in differentiating Group 3 from Group 1. Moreover, a cut-off value of >1.9 for lactate levels had 68% specificity and 60.61% sensitivity in differentiating Group 3 from Group 1, but lactate level was not found to be a meaningful parameter in differentiating Group 3 from Group 2. The results of the ROC analysis for laboratory parameters used in differentiating the groups from one another are given in Table 3.

Table 1. Basic data for patient groups

	Group 1	Group 2	Group 3	p
n (K/E)	50.00 (28/22)	35.00 (19/16)	33.00 (20/13)	0.862
Year*	67 (25-95)	70 (31-90)	72 (32-89)	0.916
BMI (kg/m2)*	28.53 (25.83-31.89)	26.430 (24.3-30.82)	29.12 (26.86-35.185)	0.30
Wells score*	**6.00 (4.50-8.00)**	**4.50 (3.00-5.00)**	**5.5. (4.12-8.00)**	**0.001**
WBC (103/ mm3)*	**10.485 (8.20-13.50)**	**8.15 (4.91-11.18)**	**8.57 (6.20-11.28)**	**0.005**
HGB (mg/dL)*	13.45 (12.0-15.0)	13.1 (11.75-14.25)	12.9 (11.60-14.07)	0.419
HCT (%)*	41.55 (36.5-46.9)	40 (37.17-42.77)	39.1 (35.62-43.95)	0.297
Lymphocyte (10e3/µL)*	**1.895 (1.25-2.31)**	**0.99 (0.57-1.68)**	**1.47 (0.89-1.98)**	**<0.001**
Neutrophils (10e3/µL)*	**7.56 (5.64-11.33)**	**6.46 (3.41-7.45)**	**6.06 (4.09-8.42)**	**0.016**
PLT (103/ mm3)*	228.50 (187.0-282.0)	238.0 (183.0-348.5)	202.0 (165.5-255.2)	0.275
aPTT (sec)*	24.8 (20.5-31.4)	22.4 (20.27-26.87)	22.6 (20.20-26.57)	0.416
PT (sec)*	13.80 (12.60-14.90)	12.90 (12.20-14.22)	14.10 (12.90-14.90)	0.052
INR*	1.13 (1.02-1.22)	1.05 (0.99-1.15)	1.15 (1.03-1.22)	0.043
Urea (mg/dL)*	43 (32.0-55.0)	39 (30.00-57.25)	43 (36.75-63.00)	0.323
Cre (mg/dL)*	0.995 (0.820-1.170)	0.98 (0.75-1.20)	0.96 (0.67-1.10)	0.284
CRP (mg/dL)*	44.8 (13.7-94.5)	32.3 (15.67-109.50)	34.7 (16.92-121.00)	0.989
Procalcitonin *	0.14 (0.10-0.42)	0.23 (0.10-0.56)	0.17 (0.10-0.56)	0.522
DIMER (mg/L)*	**4235 (3200-6850)**	**1890 (565-3425)**	**6900 (3917.50-11517.50)**	**<0.001**
Lactate*	**1.8 (1.22-2.20)**	**2.7 (1.60-3.20)**	**2.2 (1.600-3.240)**	**0.001**

* Median (IQR), Group 1: Covid-19 (-) and PE (+), Group 2: Covid-19 (+) and PE (-) Group 3: Covid-19 (+) and PE (+)

Discussion

This study found significant differences between patients who had COVID-19 combined with PE and patients who had PE alone in terms of lymphocyte, neutrophil and lactate levels, but no significant differences in WBC and D-Dimer levels. Comparison of patients with both COVID-19 and PE with COVID-19 (+) patients found significant differences in only D-Dimer levels, but no significant difference in WBC, lymphocyte, neutrophil or lactate levels.

Some studies have shown that infectious conditions may be associated with the development of venous thromboembolism (VTE) [7,8] and that a significant proportion of patients with PE have underlying respiratory tract infections [12,13]. Some of the most frequently reported biological anomalies in patients with COVID-19 include elevated levels of inflammatory markers, such as C-reactive protein, D-Dimer, ferritin and interleukin-6 [14,15].

A vast majority of patients with COVID-19 have been found to exhibit unusually high levels of D-Dimer, and high levels of D-Dimer caused by both cytokine storm and clotting activation have been associated with increased mortality [5,14,16]. Patients with COVID-19 who had elevated D-Dimer levels (>1000 ng·mL−1) at the time of presentation have been reported to

Table 2. Pairwise comparison of laboratory parameters found to be different among the groups

		Well score	WBC	Lymphocyte	Neutrophils	DIMMER	Lactate
Group 1	Group 2	<0.001	0.006	<0.001	0.009	<0.001	0.002
Group 3	Group 1	0.765	0.082	0.019	0.028	0.053	0.029
	Group 2	0.008	0.429	0.233	0.723	<0.001	0.466

Group 1: Covid-19 (-) and PE (+), Group 2: Covid-19 (+) and PE (-) Group 3: Covid-19 (+) and PE (+)

Table 3. Results of ROC analysis for the use of D-Dimer and lactate in differentiating the groups

			Cut off	AUC	p	Sensitivity	Specificity	95% CI
Group 1	Group 2	D-Dimer	>2590	0.782	<0.0001	78.00	71.43	0.680 - 0.865
		Lactate	≤2.5	0.718	0.0002	86.00	51.43	0.610 - 0.810
Group 3	Group 1	D-Dimer	>9670	0.683	0.0040	39.39	96.00	0.571 - 0.781
		Lactate	>1.9	0.669	0.0076	60.61	68.00	0.557 - 0.769
	Group 2	D-Dimer	>3640	0.870	<0.0001	81.82	80.00	0.766 - 0.939
		Lactate	≤4.33	0.555	0.4411	93.94	20.00	0.429 - 0.675

Group 1: Covid-19 (-) and PE (+); Group 2: Covid-19 (+) and PE (-); Group 3: Covid-19 (+) and PE (+)

have an 18-fold higher risk of in-hospital mortality than those with normal D-Dimer levels [15]. In a study by Mouhat et al., they compared data from 44 patients who developed PE out of 162 patients with COVID-19, and ROC curve analysis identified an optimal cut-off value of 2590 ng·mL−1 for D-Dimer to predict CTPA-approved PE in patients with severe COVID-19 with high accuracy: AUC 0.88 (95% CI 0.809–0.932, p < 0.001); sensitivity % 83.3 and specificity % 83.8 [17]. In a multi-centre study involving 333 consecutive SARS-CoV-2 patients admitted to seven hospitals in Italy, Loffi M et al. [18] compared data from PE (n = 109) and Non-PE (n = 224) patients and found that patients with PE with concomitant SARS-CoV-2 had significantly higher levels of D-Dimer, WBC and hemoglobin compared with non-PE patients. The present study found that a cut-off value of >3640 for D-Dimer exhibited 81.82% sensitivity and 80.00% specificity in the differentiation of Group 3 and Group 2. On the contrary, a cut-off value of >9670 for D-Dimer had 39.39% sensitivity and 96.00% specificity in differentiating Group 3 from Group 1.

Lactate is an indicator of insufficient tissue perfusion and has been shown to be correlated with disease severity in a variety of shock conditions, from sepsis to trauma and to cardiogenic shock [19,20]. Hyperlactataemia is a marker of tissue hypoxia when anaerobic tissue metabolism is increased, especially in anemia, fever with increased oxygen demand and infections with microvascular obstruction. Hyperlactataemia has been traditionally associated with poor outcomes in critically ill patients, and lactate is considered one of the most important biomarkers for disease severity in patients with sepsis [21,22]. Although COVID-19 is predominantly a pulmonary disease, it is also associated with end organ damage, systemic dysfunction, thrombosis and ischaemia [23]. A retrospective observational study on patients with COVID-19 pneumonia found lactate levels to be associated with poor clinical outcomes [24]. In another study, Valevan et al. [25] reported significantly higher serum lactate levels in hospitalized patients with COVID-19 compared with outpatients. The present study found that lactate levels were higher in patients with COVID-19 than in patients with pulmonary embolism (PE). It was also found that Group 3 had significantly higher levels of lactate compared with patients in Group 1, but there was no difference between Group 3 and Group 2.

Conclusion

As a result, COVID-19 leads to increased incidence of PE. In addition to clinical data, D-Dimer and lactate levels can be used in the differentiation of these patients.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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